Mechanical Transition from α-Helical Coiled-Coils to β-Sheets in Fibrin(ogen)

Supporting Information

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Short Title: α-to-β phase transition in fibrin(ogen)

Structural Models: Atomic structural models of human fibrinogen were obtained using X-ray structures from the Protein Data Bank (PDB: entry 3GHG). We used the whole human fibrinogen molecule (Fg, see Fig. 1), and its coiled-coil portions, namely the double coiled-coil part including the central domain (DCC) and the single coiled-coil (SCC). To construct the DCC portion of Fg, the full-length molecule was truncated at the residues Cysβ197 and Cysγ139 in the Bβ- and γ-chains, which correspond to the distal disulfide rings at both ends. The X-ray structure of the Fg molecule is formed by 1,913 amino acid residues (19,939 atoms in united-atom CHARMM19 force field or 30,157 atoms in total). The DCC portion contains 878 amino acid residues (8,870 united atoms and 14,178 atoms in total), which include Aα27-200, Bβ58-197, and γ14-139. The SCC portion was obtained by truncating the DCC construct and by removing the central domain (residues up to a central disulphide rings, namely Aα27-44, Bβ58-75, γ14-18). We retained only one of the two symmetric parts of the coiled-coils. The SCC construct contains 399 amino acids (4,054 united atoms and 6,492 atoms in total), namely Aα45-200, Bβ76-197, and γ19-139. The structures were minimized using the steepest descent algorithm, and heated and equilibrated at $T = 300$ K.

Implicit Solvent Models: In SASA and GB model, the potential energy $V = V_b + V_{nb} + V_{solv}$ includes the bonded potential V_b, the non-bonded potential V_{nb}, and the solvation potential V_{solv}. The bonded potential associated with vibrations of the covalent bonds, bending of the bond angles, as well as dihedral and improper angles is given by $V_b = \sum_{bonds} K_b (b - b_0)^2 + \sum_{angles} K_\theta (\theta - \theta_0)^2 + \sum_{dihedral} K_\phi \left(1 - \cos\left[n\phi - \phi_0\right]\right) + \sum_{imp} K_\psi (\psi - \psi_0)^2$, in which K_b, K_θ, K_ϕ, and K_ψ are the spring constants for the covalent bonds, bond angles, and dihedral and improper angles, and b_0, θ_0, ϕ_0, and ψ_0 are their equilibrium values. The non-bonded potential $V_{nb} = \sum_{i,j} q_i q_j / \left(4\pi\varepsilon_0 \varepsilon r_{ij}\right) + \sum_{ij} \varepsilon_{ij} \left[\left(R_{ij}^{\min} / r_{ij}\right)^{12} - 2\left(R_{ij}^{\min} / r_{ij}\right)^6\right]$, where r_{ij} is the distance between atoms i and j, q_i and q_j are their charges, and ε and ε_0 are, respectively, the electric and dielectric constants, accounts for the electrostatic and van der Waals interactions ($\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$ and $R_{ij}^{\min} = (R_i^{\min} + R_j^{\min})/2$ are van der Waals parameters). In the SASA model, the solvation energy is given by $V_{solv} = \sum_i \sigma_i A_i$, where A_i is the solvent-accessible surface area for the i-th atom and σ_i is the corresponding atomic solvation parameter. In the GB model, the solvation potential is given by $V_{solv} = -1/8\pi\varepsilon_0 \left(1/\varepsilon_{in} - 1/\varepsilon_{out}\right) \sum_i \sum_j q_i q_j \Big/ \sqrt{r_{ij}^2 + \alpha_i \alpha_j \exp\left[-r_{ij}^2 / \gamma \alpha_i \alpha_j\right]}$, where ε_{in} and ε_{out} are the dielectric constants for the solute and solvent, respectively, and α_i is the Born radius ($\gamma = 4$). We used the Still approximation for the Born radius, according to which the atom displaces the volume of the surrounding solute equal its Van der Waals volume.

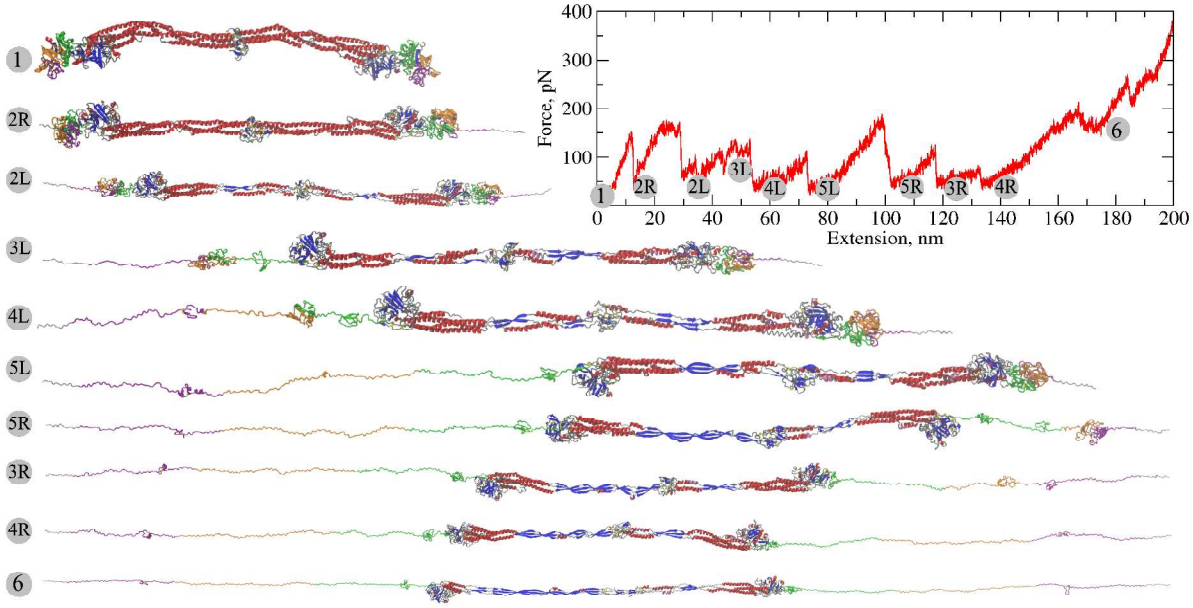

Figure S1. The force-induced unfolding transitions in the full-length Fg molecule including the symmetric left and right γ-nodules (v_f = 10^5 μm/s and k_{sp} = 100 pN/nm). This is an extended version of Figure 2 in main text. Different stages of unfolding numbered 1-6 in the force-extension profile are represented by the corresponding structural snapshots. The native folded state is represented by structure 1. The coloring scheme is same as in Fig. 2 in main text. The first two peaks (structures 2R and 2L) correspond to the β-strand pull-out. The next three force peaks (structures 3L, 4L, and 5L) correspond to the unfolding of the left (L) γ-nodule: first, unfolding of the C-terminal part occurs (structure 3L); second, the central domain unfolds (structure 4L); and third, unfolding of the N-terminal domain occurs (structure 5L). Next, the right (R) γ-nodule unravels in three steps (structures 5R, 3R, and 4R): first, unraveling of the N-terminal domain occurs (structure 5R); second, the C-terminal domain unfolds (structure 3R); third, the central domain unfolds (structure 4R). Structures 5R, 3R, and 4R show the α-to-β transitions in the coiled-coil connectors; structure 6 shows unfolding of the central domain.

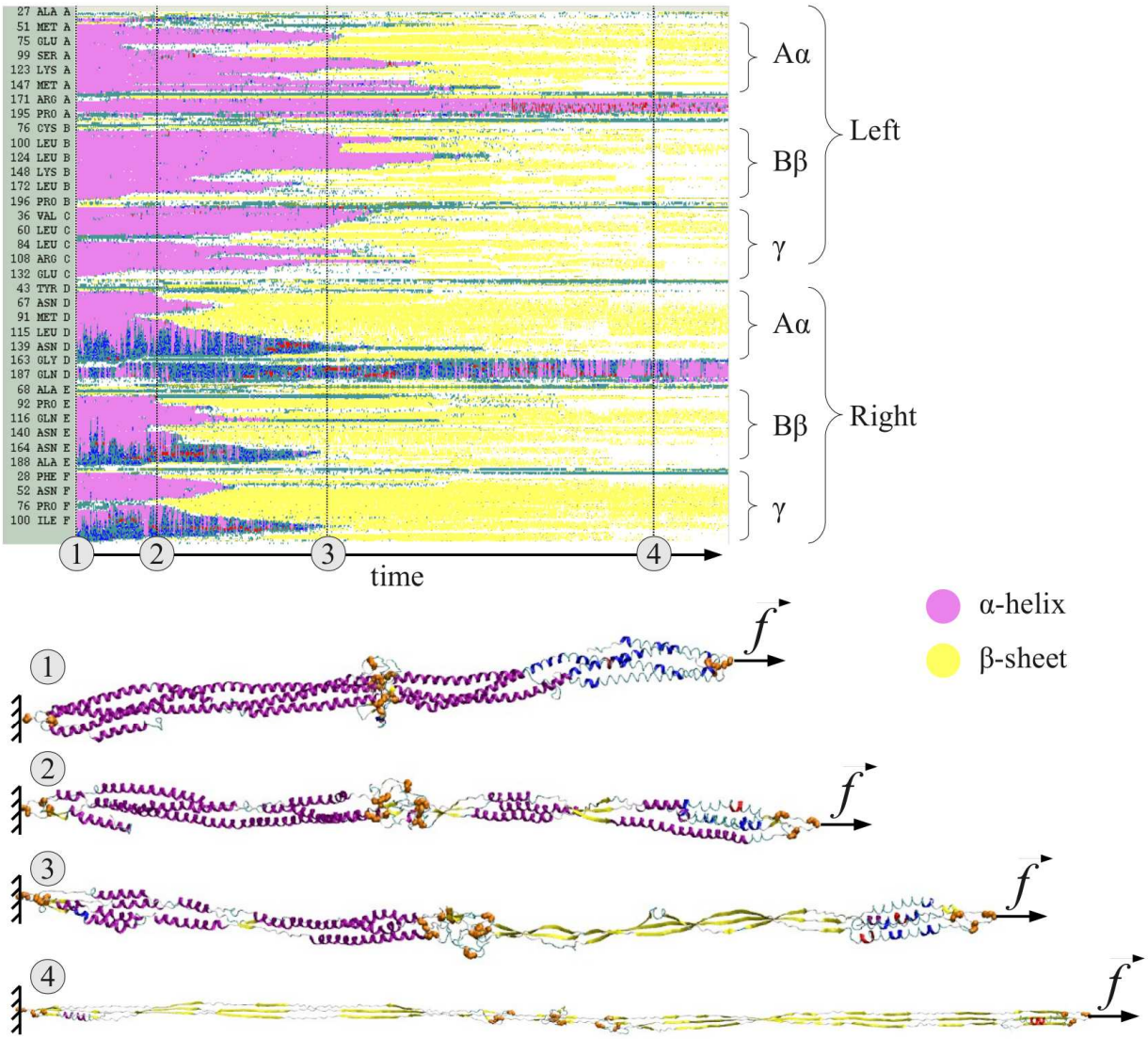

Figure S2: The α-to-β phase transition in the Fg triple-helical coiled-coils. The VMD timeline, generated using the Visual Molecular Dynamics (VMD) software shows the secondary structure elements for amino acid residues forming the double coiled-coil (DCC) construct (vertical axis) as a function of time (horizontal axis). Denotations "Left" and "Right" correspond to the symmetric left and right parts of the Fg coiled-coils. Also shown are the structural snapshots (structures 1-4), which correspond to different stages of the transition. The disulphide bonds are shown (in orange color) using the ball-and-stick representation.

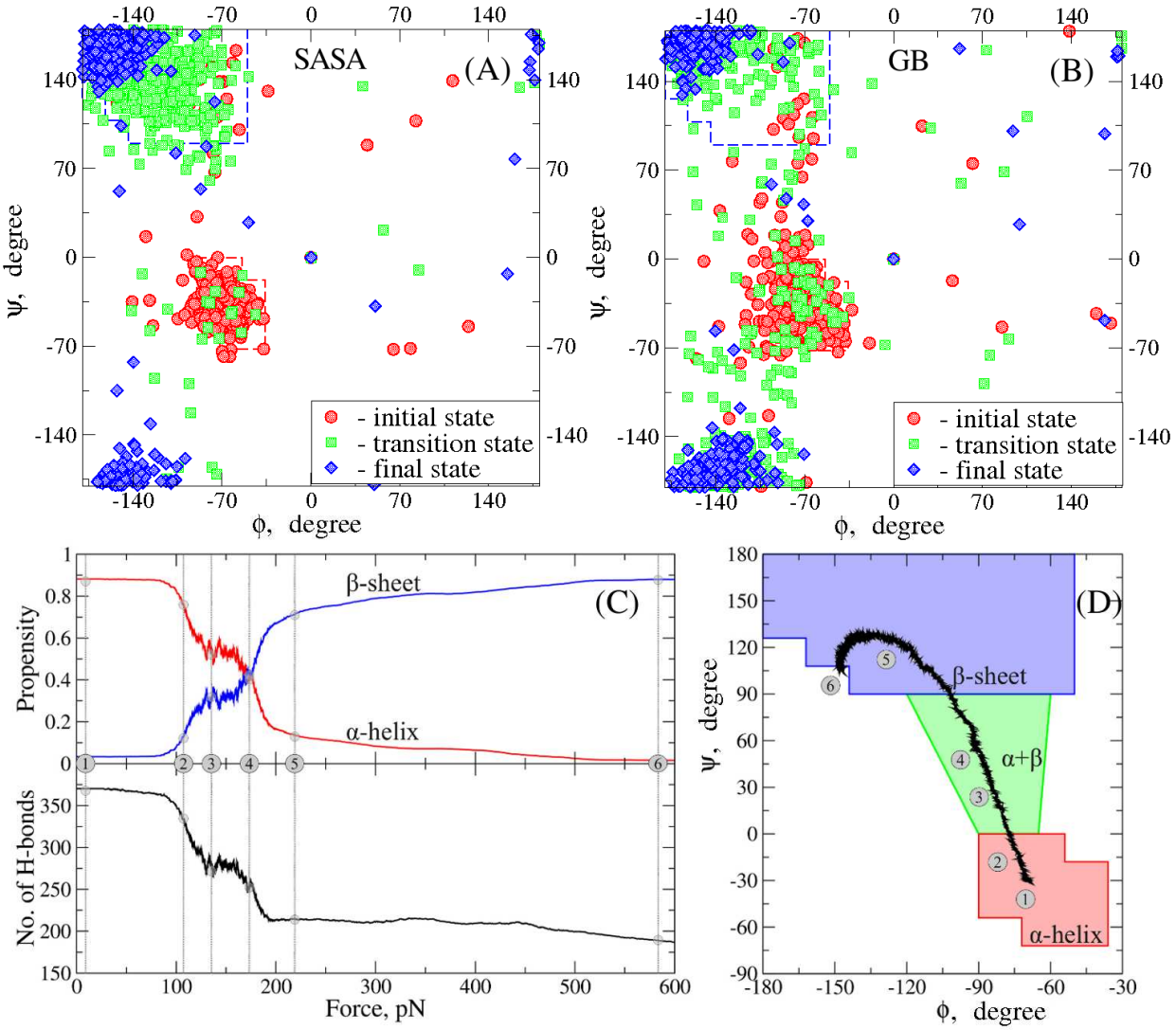

Figure S3: Analyses of the secondary structure for the α-to-β phase transition in the Fg coiled-coils (SCC portion). Panels (A) and (B): The Ramachandran map of the dihedral angles ϕ, ψ for the initial folded state, transition state, and final unfolded state, obtained from pulling simulations using the SASA model and GB model. Panel (C): The propensity of forming α-helices and β-structures, and the number of hydrogen bonds (H-bonds) as a function of the unfolding force. Panel (D): The Ramachandran plot of the average dihedral angles ϕ, ψ as a function of force. The average angles move from the α-helix region (shown in red color) to the β-sheet region (blue color) through the region of mixed α+β-character (green color). In panels (C) and (D), the structures numbered 1-6 are shown in Fig. 3 in main text.